New regulation for clinical stem cell research in China: expected impact and challenges for implementation

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Commentary

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"The 2015 'draft' regulation indicates an important step toward the improved governance and review of stem cell clinical research and applications in China."

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On 22 August 2015 the Chinese National Health and Family Planning Commission (NHFPC; the former Ministry of Health, MOH) have issued the long awaited 'draft' regulation on clinical research and applications that involve human stem cells [1–3]. In China, regulation usually starts out as a draft or trial regulation. A draft regulation should be regarded as valid as formal regulation, but it is flexible enough to leave space for change. The document announces the central elements of a regulatory foundation for the clinical translation of stem cell-based medicinal products and procedures. What does China's future regulation for clinical stem cell trials look like? What challenges can be expected with regard to its implementation? And what impacts will the regulation have for domestic researchers, clinics and corporations in China and at an international level?

Overview of the draft regulation

The draft regulation applies to the clinical use of human autologous and allogeneic stem cells that are manipulated *in vitro*, with the exception of the routine transplantations of hematopoietic stem cells and of clinical trials that use stem cells that are affirmed as pharmaceutical products. Stem cell treatments have to pass through methodical clinical studies and follow from systematic preclinical evidence. These trials must comply with the Chinese 'Quality Control Standards for Clinical Drug Trials' (the Chinese good clinical practice standards), which has guided the approval of new drugs by the China Food and Drug Administration (CFDA) since 2007. Furthermore, first-in-human clinical trials must be based on systematic evidence of preclinical research proving the therapeutic value and safety of a candidate treatment in appropriate animal models.

The standards and technical procedures for the collection, manufacturing and storage of stem cells for clinical use are laid down in the 'Stem Cell Preparations Quality Control and Preclinical Research Guidelines', a supplementary document published by the CFDA, which also specifies the required criteria for safety and efficacy assessment in the context of preclinical studies. Only level 3 hospitals – the highest ranked hospital category in China – are permitted to conduct stem cell clinical trials. To qualify, such hospitals must have established institutions for research, healthcare and teaching, and be in possession of the relevant professional qualifications. Hospitals must have ethics and academic committees capable of dealing adequately with adverse effects and preventing high-risk applications. Moreover, hospitals are required to establish stem cell preparation facilities that are compliant with international GMP standards.

Investigators applying for stem cell clinical trials must do so at provincial branches of the NHFPC and CFDA, and register the trials

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online at the Chinese Medicine Registry and Management System. The NHFPC and CFDAs will jointly review the projects at a provincial level with the help of specifically formed expert committees. These committees do not only review incoming applications but also will conduct on-site verification and evaluation of academic institutions, ethics committees and project management. If a clinical trial application is accepted, Phase I of the trial can go ahead. Clinical trial progress reports must be submitted to the authorities on a regular basis, and after each phase investigators need to report the research results to the provincial agencies. Based on these reports, decisions are made about progression to the next phase and ultimately about routine clinical application.

The regulation seeks to protect the interests of patients in the following ways. First of all, clinical investigators may not charge money for patients taking part in clinical studies, and hospitals are not allowed to advertise stem cell trials as treatments. Hospitals are required to fully inform patients of the potential risks of the research involved, and to arrange insurance coverage for human subjects for projects involving a high level of risk. In case of emergency, life-saving facilities need to be in place. Moreover, serious adverse events must be reported to the hospital ethics committee and the provincial health authorities, and will result in the immediate halt of the research project and withdrawal of approval for the application of the stem cell therapy concerned.

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Stem cell clinical trials must be conducted in accordance with the '2007 Interim Regulation on the Review of Biomedical Research Involving Human Subjects' of the MOH (now NHFPC), and the 'Drug Administration Law', issued by the MOH in 2001. Clinical trials using human embryonic stem cells must harvest and process the cells in line with the 'Guiding Principles for the Ethics for Human Embryonic Stem Cell Research', a joint regulation issued in 2003 by the Ministry of Science and Technology and the MOH. With the new draft regulation stem cell-based treatments are no longer regulated as class III medical technology in accordance with the 2009 regulation for clinical stem cell applications [4], which indicates that the former regulation is no longer valid.

Medical institutions and staff who violate regulatory provisions are directly held responsible in accordance with specifically designed penal procedures. The provincial branches of the NHFPC and CFDA have the authority to suspend stem cell trials and to punish investigators and staff in line with appropriate laws and regulations.

Commentary

China has invested heavily into stem cell medicine in recent years. This has resulted in a growing body of publications and the development of new candidate therapies [5]. Simultaneously, due to a permissive regulatory environment for clinical stem cell applications, the country has witnessed the mushrooming of commercial stem cell clinics. Between 2002 and 2012, China became a global hub for the sale of unproven clinical for-profit interventions [6]. A first attempt to control this situation was undertaken in 2009 in the context of a new regulation for medical technologies [7]. However, because of disagreements within the health authorities on feasible implementation pathways, this regulation was never enforced for stem cell research and the number of unproven stem cell interventions was widely reported to grow [6–8]. In 2012, the MOH undertook a renewed regulatory effort by introducing a notification, which stipulated that all medical institutions without prior approval from the MOH or the CFDA must stop clinical stem cell procedures. This notification had limited effect, mainly on state-supported scientific institutions. An article in *Nature* reported that 3 months after the ban, numerous clinics in China were continuing their services [9]. Then, in March 2013, the NHFPC published three inter-related draft regulations for public comments. These documents announced stringent controls on experimental stem cell interventions and emphasized clinical translation through systematic clinical trials overseen by the Chinese health authorities.

Elements of the 2013 regulation have now been incorporated in the regulatory documents published in August 2015. The 2015 'draft' regulation indicates an important step toward the improved governance and review of stem cell clinical research and applications in China. With the enforcement of systematic clinical studies required to comply with scientific principles, standardization, transparency and the improved protection of research subjects, the CFDA and NHFPC have established a framework intended to cater to the needs of researchers in China and internationally. The regulation rejects the use of unproven experimental for-profit interventions with stem cells [5], while introducing a clear strategy toward more responsible forms of clinical translation. The prohibition to advertise unproven stem cell treatment and charging patients for taking part in experimental studies alone could potentially result in the permanent halt of experimental for-profit interventions in a large number of hospitals that have profited

from unclear regulations for years [8]. Institutions that work under the publicized rules can be expected to raise methodological standards, improve the validity of research data and subject patients to less risk.

However, the actual impact of the regulation depends on its enforcement and implementation. By sharing administrative duties for review and certification of clinical stem cell research and applications between provincial NHFPC and CFDA branches, and by training specialist staff and expert committees to operate at the provincial level, China's health authorities create a regulatory infrastructure that promises to hit its target. The document's grounding in the country's 'Drug Administration Law' and the backing of its stipulations by punitive measures reinforces this impression. Implementation, nonetheless, can be expected to be a difficult and gradual process, with several challenges along the way. A first challenge will be to train sufficient numbers of staff, and to recruit well-qualified experts for independent review, so that incoming applications can be dealt with in a reliable and simultaneously efficient way. A further challenge concerns the geographical size of China, the country's large number of medical institutions, and the lucrative business opportunities that have evolved in the stem cell field in recent years [10]. In the light of the well-established national and international networks of for-profit stem cell therapy providers in China [7], it will be difficult to control for-profit stem cell clinics. The problem of implementing the regulation to established institutions that seek to approve stem cell clinical trials is different from that of controlling stem cell clinics. While the new draft regulation delegitimizes unapproved for-profit stem cell interventions and provides a legal basis to close down such clinics, it does not provide concrete details on how the enforcement of such controls might occur. While the Chinese authorities in the last years have sporadically clamped down on for-profit stem cell clinics [7], it is unclear whether the resources, administrative infrastructure and the political will can be mobilized to counter these clinics on a large scale and on a nation-wide level. Enforcement of the regulation in the context of level 3 hospitals, on the other hand, can be expected to be successful: China's elite stem cell researchers have long-since demanded a kind of regulation that can legitimize their research and resulting clinical applications. It remains to be seen, however, how tightly oversight procedures for clinical stem cell applications will be organized and whether the number of staff and available resources will be sufficient to assure dependable implementation.

Moreover, variation can be expected in the interpretation of regulation and policies among the provinces. Will these divergent interpretations thwart homogenous implementation? Despite possible variation across provinces, it is clear in the draft regulation that all research and commercial activities fall under the responsibility of the main units of the NHFPC and the CFDA in Beijing, which prohibit unauthorized for-profit interventions at the national level. Exemptions from the national standard at the provincial level (which has proven a hindrance for the effective regulation of autologous stem cell treatments in the USA [11]) are not possible.

It is also not clear to what extent the regulation affect practices in army and police hospitals, which have their own regulatory bodies and where much of the commercial stem cell activities have been located in recent years [12]. Much will depend on the political prioritization of tackling all experimental stem cell therapy providers, ranging from small for-profit providers to powerful military organizations.

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The promise of greater dependability of approval procedures for the clinical development of stem cell treatments and greater compatibility with international procedures should be a relief to many stem cell scientists in China. The absence of a functioning regulatory framework for clinical stem cell research for many years has deprived researchers and R&D companies of the possibility to apply for the official registration of newly developed candidate treatments [6]. It has also limited the opportunity for building international clinical research collaborations [13]. By introducing systematic approval procedures for stem cell clinical trials the forthcoming regulation will strengthen domestic innovation trajectories, facilitate collaborations with foreign researchers and also allow for joint applications for the approval of candidate therapies at drug regulatory authorities in China and in other countries.

The draft regulation's commitment to systematic preclinical studies, clinical trials, reliable quality controls, the Chinese good clinical practice standards, Good Manufacturing Practice (GMP) and external review by independent expert committees promises to create congruence with both, the benchmarks set out in the 'Guidelines for the Clinical Translation of Stem Cells' of the International Society for Stem Cell Research [14], and the standards for clinical stem cell research handled by the US FDA and the EMA.

Open questions

The new draft regulation provides a basis to define experimental for profit interventions with stem cells in China as illegal and to investigate and punish stem cell clinics

that operate outside the supervision of the NHFCP and the CFDA. The focus of this new regulation, however, is exclusively on the governance of clinical research. It does not stipulate any details on how the transition from clinical trials to routine clinical use and market approval shall be handled. This leaves many questions to be answered that will be crucial for corporations and international collaborations that strive for the joint application of stem cell treatments at drug regulatory authorities in China and other countries. Because information on marketing conditions is absent in the publicized regulation, it is extremely difficult to discuss its implications for international collaborations. A possible explanation to the lack of information on market approval in the current regulation is that no agreement on this point has been reached yet between involved stakeholders.

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Unclear is also what procedures will be handled for the clinical use of stem cells that are affirmed as pharmaceutical products, and also what criteria the NHFCP and the CFDA handle in order to define pharmaceutical stem cell products. Clearly designated subcategories of different types of stem cell interventions have not yet been published. However, such definitions will be of crucial importance to determine the relevant regulatory authority (the NHFCP or the CFDA, or different subunits). The fact that the CFDA is closely involved in the drafting and implementation of this regulation suggests that at least some stem cell based applications will be classified as medicinal products. No matter how, the fact that this important point remains undefined suggests that harmonization with regulatory agencies in the USA, Europe and other highly developed countries is still a long way off. These uncertainties might cause confusion for biotech companies, especially those that produce stem cells as quantifiable batch products from a single cell line, as for instance Geron has done with its human embryonic stem cell product [11]. Another question is what type of clinical studies the NHFCP and CFDA require to allow the go-ahead from clinic to the market and routine use. While in a former, now invalid draft of the new regulation that was issued for public consultation in 2013 it was stated that systematic controlled Phase I–III trials would be required [15], the current regulation only speaks of clinical trials that shall be conducted according to scientific principles. Do China's health regulators leave this question deliberately open, so as to have the flexibility to follow the current Japanese model rather than the USA or EU model, which allows for conditional and time-limited market approval after successful clinical studies with relatively small number of patients [16]? Another issue that remains unclear is whether the new regulation in China leaves space for the conduct of experimental clinical interventions with stem cells outside of the format of the clinical trial (for instance as a 'last resort' treatment in individual patients after all existing interventions have failed) and how these forms of clinical experimentation will be reviewed and approved. A further question is how the regulation will impact the affordability of stem cell trials. The requirement of systematic preclinical research, the availability of GMP laboratories and clinical translation through systematic clinical trials will significantly increase the costs of clinical translation. Accordingly, the introduction of the new regulations may have drawbacks for less well-endowed research institutes [7]. With increased costs and a system that allows clinical studies solely in qualified tier three hospitals, only a limited number of investigators and research institutions will be enabled to conduct clinical stem cell trials. The resulting unequal access to financial resources may redefine opportunities to clinical innovations in the stem cell field. It remains to be seen whether this new situation will reignite a new brain drain to the private sector or abroad.

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